NEUROGENIC IRREGULARITIES OF THE HEART IN ADULTS.

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FLUCTUATION in the activity of the sino-atrial node in children is well known and is regarded as an expression of instability of the incompletely developed nervous mechanism of the heart, and hence is without significance. Concerning sinus irregularity in adults, clinical opinion varies. According to Mackenzie[1] its presence indicates that the heart is healthy; the individual showing it is never conscious of the irregularity; certain neurotic individuals may show it late in life. Norris and Landis[2] state that its recognition becomes important mainly for the purpose of excluding serious forms of arrhythmia. Eppinger and Hess[3] consider all sinus arrhythmia occurring after the age of fifteen years a symptom of vagotonia, that having been defined as a functional autonomic system disease. In 1912 Windle[4] asserted that this irregularity had not yet been shown to occur in degenerative heart lesions. However, two years before, Stokes[5] reported a case of sinus arrhythmia associated with anginal attacks occurring in a woman, aged thirty-six years, who had had rheumatic fever when ten years of age and who showed signs of heart involvement.

On the other hand, Thorne[6] after observing cases of sinus arrhythmia in soldiers concluded that the presence of sinus arrhythmia, "which indicates an irregular cardiac dilatation," is not an absolutely normal phenomenon and that most people in whom this irregularity is present are more liable to suffer from a cardiac breakdown under mental or physical strain than those who have a perfectly regular pulse. Danielopolu and Heitz[7] assert that many clinicians have established a relation between weakness of the circulation and the presence of sinus arrhythmia, and they report three cases of respiratory arrhythmia in association with high systolic blood-pressure. In a more recent paper Aalsmeer[8] has reviewed the cases of Laslett, Wenckeback and Vaquez and Esmein in which marked sinus arrhythmia was associated with symptoms of cerebral anemia, and he cites the case of a young soldier with an apparently normal heart in whom a sinus arrhythmia occurred in a simple tachycardia. As the vagus and accelerator systems seemed to be functioning perfectly, he concluded that the cause of the arrhythmia was to be sought in changes in the reacting organ. He likewise says that respiratory arrhythmia cannot be regarded as a sign of a good heart.

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[1] Principles of Diagnosis and Treatment in Heart Affections, London, Oxford Press, 1916.

[2] Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1917.

[3] Vagotonia, New York, Nervous and Mental Disease Publishing Company, 1917.

[4] A Note on the Diagnosis of Sinus Arrhythmia, Quart. Jour. Med., 1911–12, v, 326.

[5] Sinus Arrhythmia Associated with Anginal Attacks, Heart, 1910, i, 297.

[6] The Clinical Significance of Sinus Arrhythmia, Practitioner, 1916, xcvii, 274.

[7] Sur La Présence d'Une Arythmie Sinusale Chez Quelques Hypertendus, Arch. Mal. du Cœur, 1914, vii, 449.

[8] Over Sinus Arrhythmie, Nederland. Tijdschrift voor Geneeskunde, 1919, lv, 825.

In the early clinical literature sinus arrhythmia has been attributed almost solely to variations in vagal inhibitory tone, usually dependent on phasic respiratory changes. Lewis, however, has shown sinus arrhythmia in a normal child not of respiratory origin. Aalsmeer has argued for the possibility of heightened accelerator tone as a cause of the arrhythmia. That the pacemaker is controlled by a dual nerve supply has long been known, and in 1897 Hunt[9] presented further evidence for the view that the inhibitory and accelerator nerves are mutually antagonistic. Later the work of Cohn showed that the right vagus was limited for the most part to the sinus node, and Rothberger and Winterberg showed a similar distribution for the right accelerator. Thus it is obvious that the sinus activity at any moment is a resultant of the two oppositely acting sources of innervation and that the cause of variation may be one of four possibilities: an increase or a diminution of vagal tone; an increase or diminution of sympathetic tone.

But in cases of variation of sinus activity in man there seems to be no way to show conclusively in which system fluctuation occurs. The conclusion of Aalsmeer that if with the faster rhythm following exertion the arrhythmia disappears the sympathetic system works well and the vagus falls short is open to criticism, for when the accelerator nerves are severed in dogs exercise promptly causes as great an increase in rate as in normal animals. Applying this knowledge to man the increase in heart-rate following exercise is to be attributed to diminution of inhibitory tonus. That in cases showing excessive activity in either the vagus or sympathetic system the overactive system might be in unstable equilibrium which would cause an arrhythmia seemed at first an attractive hypothesis, but sufficient facts were not found to support it, especially the behavior under atropin. Sinus arrhythmia is frequently seen in hyperthyroidism, in which condition excessive sympathetic activity is at present believed to occur. Fig. 1 is an example. The average pulse-rate was 90 and the *R–R* interval varied between 0.6 and 0.82 seconds. Fig. 2 is from a patient suffering from an acute toxic goiter; during the slower rate of 70 the *R–R* interval varied between

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[9] Direct and Reflex Acceleration of the Mammalian Heart with Some Observations of the Inhibitory and Accelerator Nerves, Am. Jour. Physiol., 1899, ii, 395.

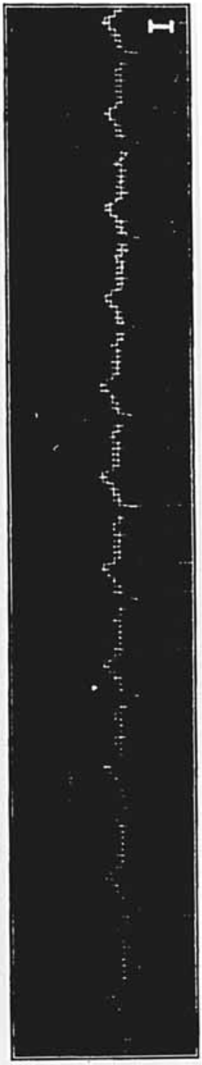

FIG. 1.—From a case of hyperthyroidism; average pulse-rate, 90.

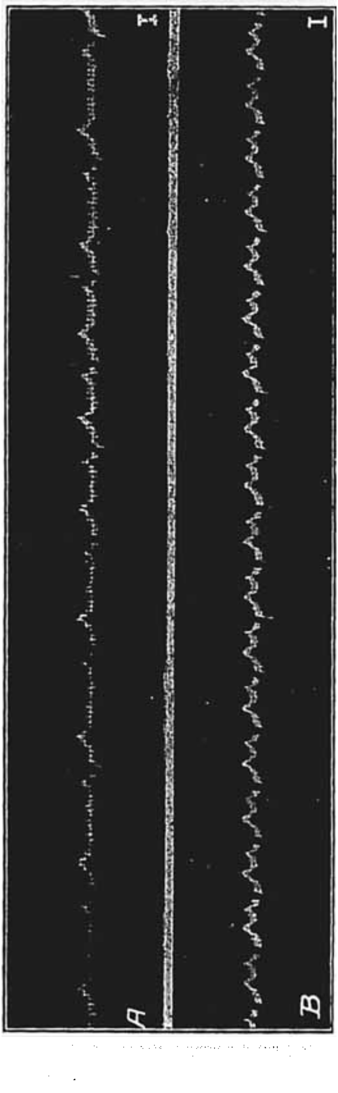

FIG. 2.—*A*, slow rate with sinus arrhythmia; *B*, simple tachycardia, rate 140; taken during an attack of palpitation.

0.6 and 1.04 seconds. Frequently attacks of palpitation occurred in which there was a simple tachycardia, with a rate of 140. Either as a result of diminution of vagus tone or an actual increase of sympathetic tone the accelerator system gained the upper hand, but no arrhythmia is present. Aalsmeer has also stated that sinus arrhythmia seen during a high rate after atropin is due to vagus influence. If such occurs after sufficient atropin to paralyze the vagi it would rather be due to fluctuation in accelerator tone. No example is available. It is customary to attribute the sinus arrhythmia seen in clinical conditions characterized by excessive vagal activity to fluctuation in inhibitory tone because the arrhythmia disappears after removal of vagus influence. However, one sees similar clinical pictures with vagus bradycardia but without arrhythmia. From the facts at hand the only tenable conclusion seems to be that sinus arrhythmia does not result directly from a preponderance of activity of either nervous system but is an expression of inequality of the antagonistic forces and is probably brought about by a periodic increase in the activity of the weaker system to restore, if possible, a more perfect balance. Such a concept is in a measure comparable to the familiar ventricular "escape" from prolonged vagus stimulation.

Knowledge of the factors which may modify accelerator tone is far from complete. Hunt regarded all cases of rapid heart action as due to diminution of activity of the cardio-inhibitory center and found no evidence that the accelerator nerves ever responded to reflex activity. But Hooker[10] has shown that when the heart is kept slowed by stimulation of the peripheral ends of the cut vagi various sensory stimuli would produce reflex acceleration. From the newer work of Cannon and others it would appear that in man reflex accelerator stimulation may be emotional or result from stimulation of sensory nerves.

Factors which may result in alteration of inhibitory tone are well known; the center may be acted upon by impulses from higher levels in the brain, impulses transmitted by various afferent nerves or by changes in the composition of the blood. All medullary centers are highly sensitive to changes in the H ion concentration; an increase causes stimulation of the inhibitory center. Reflex inhibition may result from stimulation of various sensory nerves or surfaces and the afferent fibers from the thoracic and abdominal viscera. The most important afferent nerves which affect reflexly the action of the heart, says Starling,[11] come from the heart and aorta itself. Einthoven[12] has shown electrical changes in the afferent fibers of the vagus due to each heart-beat. Although the heart contains no true sensory nerves it is admitted by physiologists that in pathologic states impulses may arise in the heart which will result in sensations of pain, usually referred to the cutaneous areas supplied by the second and the third dorsal roots. That under certain abnormal conditions of the myocardium afferent impulses arising in the heart might bring about disturbances of the cardiac mechanism by altering the inhibitory tone would seem to be well within the range of possibilities.

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[10] May Reflex Cardiac Acceleration Occur Independently of the Cardio-inhibitory Centre? Am. Jour. Physiol., 1907, xix, 417.

[11] Human Physiology, Philadelphia, Lea & Febiger, 1915.

[12] On Vagus Currents Examined with the String Galvanometer, Quart. Jour. Exp. Physiol., 1908, i, 243.

Sinus arrhythmia is seen in a variety of clinical conditions. It frequently occurs following recovery from failure of the reserve force of the myocardium, and it is common after febrile diseases, especially those in which the heart may be affected, rheumatic fever, pneumonia, diphtheria. For years Mackenzie has taught that the presence of this irregularity after a febrile illness indicates that the heart has escaped infection because, he argues, irritation within the myocardium and apparent vagus activity are incompatible, since during the febrile state when a rapid rate is maintained the vagus is unable to assert itself. Such a theory assumes myocardial irritation as the sole cause for the rapid rate. It is obvious that the more rapid the rate, the less will be the opportunity for the occurrence of an irregularity; a fibrillation under atropin at a rate of 200 will appear surprisingly regular. On purely theoretical grounds sinus arrhythmia might be considered an expression of myocardial irritation, variations in the afferent impulses manifesting themselves in unstable inhibitory tone. As far as rheumatic fever is concerned, when one considers the frequency of involvement of the heart, the incidence being about 55 per cent., and that the cardiac lesion is seldom if ever purely valvular, it may well be that sinus arrhythmia indicates not that the myocardium has escaped infection but that an irritation is present which is able to assert itself.

Reflex cardiac disturbances arising in the alimentary canal are common. But even here there is the possibility that as a result of mechanical displacement by either distended or ptosed abdominal viscera the heart may be placed at a disadvantage or the coronary circulation embarrassed and thus become the seat of abnormal reflex activity.

Sinus arrhythmia due to vagotonia is usually associated with marked bradycardia, the pulse being from 60 to 40. These patients suffer from hyperacidity and spastic constipation and show excessive moisture of palms and soles, dermographia and the varied nervous and mental reactions characteristic of that syndrome. However, vagotonia will account for but a small part of the cases of sinus arrhythmia seen at this laboratory.

The occurrence of vagal irregularities in aortic disease is not infrequent. Several illustrative cases will be cited later. Besides the usual sources of reflex vagal activity previously mentioned there remains the cardiac depressor nerve. This nerve was discovered by Ludwig and Cyon in 1866 and concerning its function in animals much is known. It is a purely afferent nerve which arises in the arch of the aorta. It contains two kinds of fibers, one of which causes reflex dilation of vessels and the other reflexly excites the cardio-inhibitory center. The fibers are carried in the vagus and the slowing is a vagus reflex which is abolished after division of those nerves. Arterial depression is a reflex by way of vasodilators. Bayliss,[13] using the string galvanometer, has shown that the nerve is excited at each heart-beat. Its function appears to be to protect the heart from too great a rise in blood-pressure. Sewall and Steiner[14] have shown that the depressors are highly sensitive to an increase of mechanical resistance to the action of the heart. Concerning abnormal functioning of the cardiac depressor in man in disease one can only speculate. But it is conceivable that in cases of pathologic changes in the aorta the endings of this afferent nerve may be the seat of abnormal impulse formation which will become manifest by disturbances usually regarded as purely vagal.

At the end of the paper may be found the histories of three adults, all past middle life, which present certain common features; each patient told of sinking spells or sensations of faintness or dizziness, and shortness of breath on exertion unaccounted for by any pulmonary condition; in each there was evidence of pathologic changes in the heart and aorta, and each showed a disturbance of cardiac mechanism due to abnormal vagal activity, the first, sinus arrhythmia, the second, partial atrioventricular block, the third, sinoatrial block. These irregularities are well known and all have been noted in hearts apparently free from disease and unassociated with any symptoms. It is not proved in these cases that the irregularity resulted in transient cerebral anemia which caused the sensation of faintness or loss of consciousness in one case, but in the search for the basis of symptoms such findings are worthy of consideration. The irregularities are regarded solely as manifestations of excessive inhibitory tonus, and it is the abnormal vagal activity which requires an explanation. To dismiss the question by saying that the affected individuals are "neurotic" is not justifiable in the presence of the physical findings. Neither psychic nor gastro-intestinal disturbances nor unusual sensory stimuli were present at the time the irregularities were recorded. The most apparent source for impulses that might result in abnormal vagal activity seemed to be in the heart or aorta in each case, and the afferent vagus fibers or the cardiac

[13] Principles of General Physiology, London, Longmans, Green & Co., 1915.

[14] A Study of the Action of the Depressor Nerve, Jour. Physiol., 1885, vi, 162.

depressor nerve provide the mechanism. The improvement following rest substantiates such a view.

The bearing of the irregularity on prognosis in such cases is problematical. The deciding factors would be the degree of dilation or relaxation of the aorta and the duration of the pause of the ventricle. The English cardiologists have called attention to the danger of premature beats in aortic disease and have found in the "compensatory pause" a possible explanation of sudden death. The same principle is involved in the cases described.

Summary. Certain facts concerning the regulation of the heart by the extrinsic nerves have been reviewed. The sinus node or "pacemaker" of the heart is under the control of the mutually antagonistic autonomic and sympathetic nervous systems, and its activity at any given moment is a resultant of these two forces. Sinus arrhythmia is an expression of imbalance between the two systems. Preponderance of either vagal or sympathetic tonus in itself such as is seen in vagotonia or hyperthyroidism does not necessarily cause arrhythmia. It appears that the irregularity results from periodic increases in the activity of the weaker system with the object of bringing about a more perfect balance.

In cases of vagal irregularities in adults it is important to determine the source of abnormal stimulation, and in considering the possibilities, it is to be remembered that the most important seat of formation of afferent impulses that may affect the cardio-inhibitory center is the heart and aorta. Just as in certain pathologic states impulses may arise in the heart which will result in sensations of pain, so it is believed that in other abnormal conditions impulses may form in the heart or aorta which, transmitted by the afferent fibers of the vagus or the cardiac depressor nerve to the inhibitory center, will become manifest as disturbances of the cardiac mechanism.

Three cases of vagal irregularities are cited, one each of sinus arrhythmia, partial atrioventricular block and sino-atrial block. In each there was evidence of pathologic changes in the heart or aorta, and the only apparent source of the excessive vagal activity was impulses which arose in those organs. Such irregularities occurring in aortic disease may be of prognostic significance as the combination of a prolonged ventricular pause and a relaxed or dilated aorta might result in a serious or even fatal cerebral anemia.

REPORTS OF CASES.

CASE I.—J. H., aged forty-eight years, formerly a cook in the navy, was admitted to the hospital on April 4, 1920, after suddenly having become unconscious and having fallen over while at work. He has had frequent attacks of what he calls giddiness. Shortness of

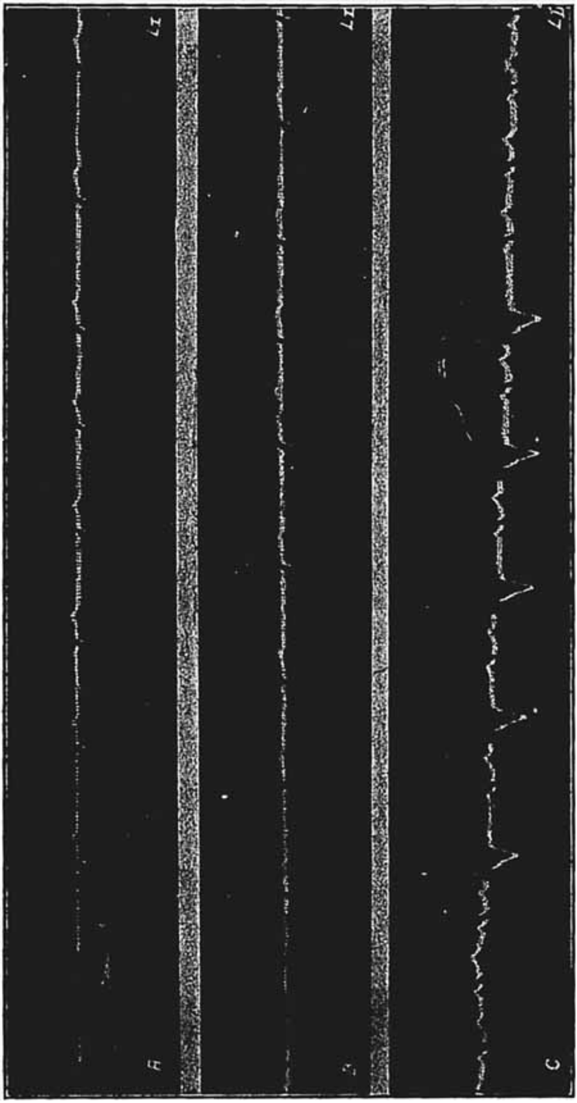

FIG. 3.—Illustrating Case I. *A*, first record; *B*, immediately after exercise; *C*, exercise three days later.

breath on exertion has been noticed for several years. He complained also of numbness in the arms and hands at times and of becoming easily fatigued.

The patient was a slender man of poor nutrition. The lips were cyanotic. Except for moderate emphysema the lungs were negative. The heart was not enlarged to percussion and the fluoroscopic examination showed a long, narrow heart; the aortic shadow was negative. At the apex the first sound was weak and the second sound was accentuated; at the aortic area a soft systolic murmur was heard and the second sound was accentuated and tympanitic. There was a marked sinus arrhythmia. Blood-pressure, 112-72. The palpable vessels were moderately thickened. The liver was palpable and tender. The extremities were cyanotic; the interossei and hypothenar eminences of both hands showed definite atrophy. The knee-jerks were hyperactive; the plantar response was normal.

The Wassermann reaction was negative and the spinal fluid negative, except the globulin test, which was reported two plus.

When first examined the heart-rate was 50 and the *R–R* intervals varied between 1.06 and 1.4 seconds. Exercise did not increase the rate and the arrhythmia remained unchanged. The almost complete disappearance of the "P" wave was doubtless also the result of vagal stimulation (Fig. 3, *A* and *B*). Following pressure on the right vagus a few right ventricular ectopic beats appeared, but there was no marked slowing, the longest pause recorded was 1.46 seconds. Left vagus pressure was without effect. The heart-rate increased to 78 and the irregularity disappeared following 0.02 gr. of atropin. After a few days of rest in bed the heart-rate increased to 70. The exercise test was repeated; this time there was a slight increase in rate, the sinus arrhythmia diminished and many ectopic beats appeared with several short periods of "coupled" rhythm (Fig. 3, *C*). The patient later resumed work in the hospital. The sinus arrhythmia persisted with an average of 80, and although the respiratory rate was 24, polygraphic records seemed to show that the irregularity was independent of respiration.

Case II.—Mrs. L., a woman, aged fifty-three years, first seen on January 21, 1920, described frequent attacks of sudden onset characterized by weakness, exhaustion, blurring of vision and a sense of sinking away; loss of consciousness, however, never occurred. At such times the pulse was said to be slow and irregular, and shortness of breath on relatively slight exertion marked. These attacks began two years ago, but during the past three months have been more frequent and the period of exhaustion lasts longer, necessitating rest in bed. There is occasionally slight "nagging" pain referred to the heart. Two years ago shortness of breath when walking up hill was first noticed. Four months ago swelling of the lower

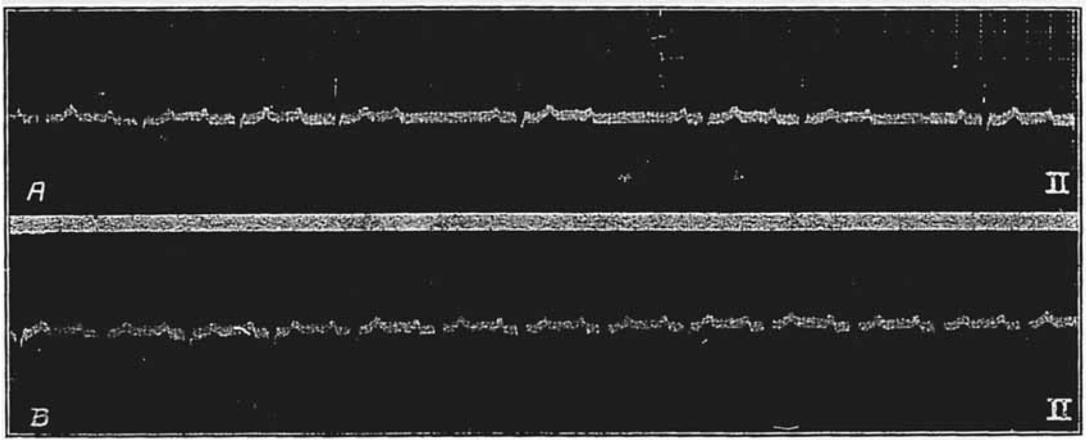

Fig. 4.—Illustrating Case II. *A*, first record; *B*, after atropin.

extremities at the end of day first occurred. Two months later she suffered from a severe attack of "bronchitis followed by congestion of the lungs."

History prior to two years is negative. In early life she had measles and scarlet fever. She has born seven children, and except for migraine attacks at the menstrual period her general health has been good. There is no evidence of syphilis.

The following are the salient facts in the physical examination: The patient was an obese woman of phlegmatic temperament. The lips were slightly cyanotic. There was no edema. The eyes were negative, except for sclerosis of the retinal arteries. The lungs and abdomen were negative. The reflexes were normal. The heart was not enlarged to percussion. The first sound at the apex was rather weak and was accompanied by a systolic murmur, not transmitted to the axilla. Over the aortic area and manubrium was heard a low-pitched, systolic murmur which was transmitted into the neck. The aortic second sound was accentuated and of a definitely tympanitic quality. The rhythm was irregular. Blood-pressure, 145–85. The peripheral vessels were moderately thickened.

The report of the roentgenologist stated: Slight degree of general cardiac hypertrophy. Aortic shadow broadened laterally. Aortitis of descending portion.

Electrocardiogram: Showed the irregularity to be due to partial heart block. There was usually progressive lengthening of the *P–R* interval through three or four successive cycles and then the impulses failed of passage and a ventricular beat was missed. Following 0.03 gr. of atropin the mechanism became normal, rate 86, *P–R* interval 0.2 seconds (Fig. 4, *A* and *B*).

After two days at rest in bed in the hospital the mechanism was normal and remained so during the period of observation.

CASE III.—Mrs. Y., aged sixty-one years, was first seen on November 3, 1919. For the past two years following "ptomain poisoning" she has noticed that her heart missed beats, and during the past year after an attack of influenza she has been subject to sinking spells which often came on after eating or after exertion. Loss of consciousness has not occurred. For some time she has suffered from agorophobia and avoided assemblies and even shopping, apparently because of a fear of fainting. She has palpitation at times and shortness of breath on exertion and indefinite pain which she said suggested the presence of glass in the heart.

Examination showed a very large heart, the apex being beyond the anterior axillary line. The aorta was somewhat broadened. At the apex the first sound was of a dull character and accompanied by a short murmur. At the aortic area was a short rough systolic murmur and the aortic second was accentuated and definitely tympanitic. The blood-pressure was 125–70.

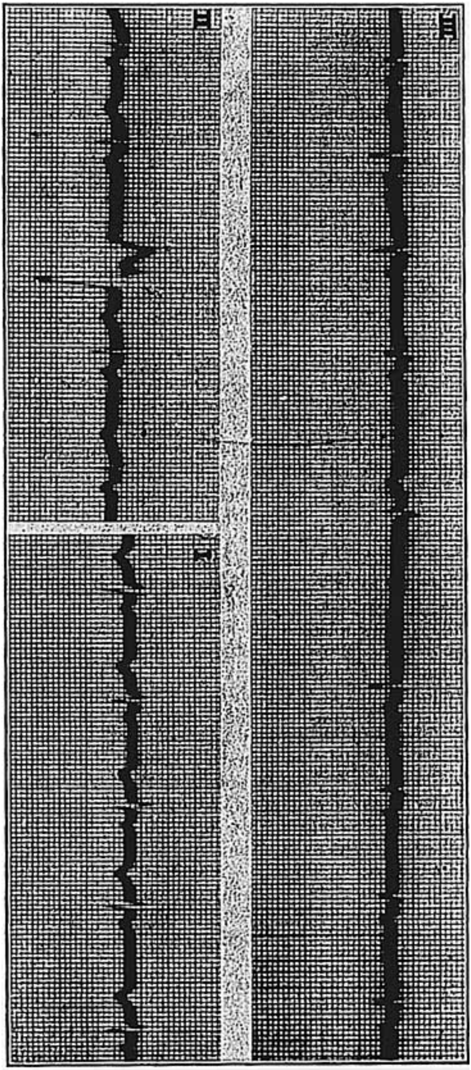

FIG. 5.—Illustrating Case III.

The electrocardiogram showed sinus arrhythmia; sino-atrial block, with a pause of 1.36 seconds from which there was an escape by an impulse originating in the upper junctional tissues, and occasional ectopic beats which arose in the right ventricle. The block occurred at irregular intervals and neither it nor the sinus arrhythmia appeared to be related respiration (Fig. 5).

This patient has been seen several times during the year. Each subsequent visit was after a rest and she was clinically improved. The sino-atrial block was observed only at the first examination.

AN EVALUATION OF THE ALLEN METHOD OF TREATMENT OF DIABETES MELLITUS.[1]

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Before the year 1915 a quite different method of treating diabetes mellitus prevailed than has since been employed. This change in method, which must be looked upon as an improvement, owes its inception to the experimental work done on dogs by Frederick M. Allen, and since confirmed by studies on humans by Allen and a number of independent workers. Among other things, Allen showed that diabetic patients could be rendered urine sugar- and ketone-free by the withdrawal of food, by fast days, and periods of underfeeding. Previous to this, other workers including Geulpa, had combined fasting with various dietary procedures, but all such work lacks the basis of scientific study. Their observations were largely clinical and uncontrolled.

Prior to 1915 the treatment of diabetes consisted chiefly in restricting the intake of carbohydrate foods, substituting for the loss occasioned thereby, additional fat and proteins. Methods were largely conjectural. Particular curative virtues were ascribed to certain foods which later investigations do not warrant. Oatmeal, skimmed milk, potato, sour milk, maple sugar and other special food cures are still in our memories. A host of drugs, ferments, animal extracts and mineral waters have similarly been exploited and have been found wanting.

Furthermore, clinical observations and statistics on diabetes made prior to 1915 are unquestionably grossly inaccurate. It has been commonly assumed by physicians that an individual whose

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[1] Presented before the Pittsburgh Academy of Medicine, Pittsburgh, Pa., April 27, 1920.